PATENT
2801-0159P

#5

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Martin J. PAGE et al.	Conf.:	
Appl. No.:	09/495,861	Group:	1644
Filed:	February 2, 2000	Examiner:	GAMBEL
For:	ANTIBODY PRODUCTION		

INFORMATION DISCLOSURE STATEMENT
(SUBMISSION AFTER FILING OF AN APPLICATION
BUT BEFORE FINAL REJECTION OR NOTICE OF ALLOWANCE
OR CONCURRENTLY WITH A RULE 53(d) CPA APPLICATION
OR WITH A RULE 1.114 RCE APPLICATION)

Assistant Commissioner for Patents
Washington, DC 20231

OFFICIAL
6/18/01 PG

Sir:

Pursuant to 37 C.F.R. §§ 1.97 and 1.98, applicant(s) hereby submit(s) an Information Disclosure Statement for consideration by the Examiner.

I. LIST OF PATENTS, PUBLICATIONS OR OTHER INFORMATION

The patents, publications, or other information submitted for consideration by the Office are listed on the PTO-1449(s), attached hereto.

II. COPIES (check at least one box)

a. ☒ Submitted herewith is a legible copy of (i) each U.S. and foreign patent; (ii) each publication or that portion which caused it to be listed; and (iii) all other information or that portion which caused it to be listed.

b. ☐ Some or all of the documents listed on the PTO-1449 are not enclosed because they were cited in the International Search Report and copies should already be in the PTO file. If copies are needed, please contact the undersigned.

III. CONCISE EXPLANATION OF THE RELEVANCE
(check at least one box)

a. ☒ **DOCUMENTS IN THE ENGLISH LANGUAGE**

The attached patents, publications, or other information in the English language do not require a statement of relevancy.

b. ☐ **DOCUMENTS NOT IN THE ENGLISH LANGUAGE**

A concise explanation of the relevance of all patents, publications, or other information listed that is not in the English language is as follows:

c. ☒ **OTHER**

The following additional information is provided for the Examiner's consideration.

The undersigned wishes to bring to the Examiner's attention various information that may be relevant to the examination of the above-identified application. It is hoped that this summary of various information will allow the Examiner to conduct a more meaningful review of the information. Copies of references and Exhibits, to which the Examiner may want to refer, are enclosed with the IDS and are listed on PTO-1449. Also enclosed are the Exhibit lists of GWI and Cabilly. If the Examiner determines that he would like to review copies of certain Exhibits that are not included with this IDS, he is requested to contact the undersigned and copies will be provided to the Examiner as soon as possible. As the Examiner has been advised, U.S. Patents 5,545,403; 5,545,404 and 5,545,403 of Page are involved in Interference Number 104,532. The '403 and '405 patents are also involved in litigation. A jury verdict in favor of Genentech verdict has been rendered and GlaxoSmithKline is appealing the jury verdict.

Prior Art References and Activities

Various activities occurred prior to the October 16, 1991 U. S. filing date of the present application that the Examiner may determine is relevant to patentability.

UAB Clinical Trials/B72.3 antibodies

In the time period between 1989 and 1991, clinical trials were conducted at the University of Alabama (UAB) by Dr. LoBuglio and others. These clinical trials used a chimeric antibody (B72.3) conjugated to a radionuclide ^{131}I that specifically bound to the antigen TAG-72 (tumor associated glycoprotein 72). Testimony was presented that the B72.3 antibody may have been expressed in and

glycosylated by CHO cells. (LoBuglio Deposition, page 48 line 17 to page 49, line 17 and page 240, line 10 to page 241, line 14.) Additional testimony regarding the B72.3 was presented at the trial in the related district court litigation (Trial Transcript 2770:15-2775:9, 2778:23-2785:1, 2815:16-2819:6, 2821:8-2822:22)

The following references pertain to mAb B72.3 and the trials at University of Alabama:

Baker, et al	1991	Antibody, Immunocongugates, and Radiopharmaceuticals, Vol. 4, No. 4 (
Bodmer, et al	1993	U. S. Patent 5,219,996
Colcher et al.	1989	Cancer Res. 49:1738-1745
Harris et al.	1990	Proc. 34th Oholo Conf, Eilat, Israel pgs. 465-477
Khazaeli et al.	1991	Cancer Res. 51:5461-5466
Khazaeli et al.	1990	HER010300098/315 Abst. Sub. 37th Ann. Mtg of Soc of Nucl. Med.
Khazaeli et al.	1990	HER010300100/317 Abst. Sub. 3rd Conf. On Radioimmunodetect…
Khazaeli et al.	1991	Can. Res. 51:5461-5466
Khazaeli et al.	1991	HER010300319 Abst. Sub. 6th Intl. Conf. On Monoclonal Anti. Immunoconj.
Khazaeli et al.	1992	J. of Clin. Immunol. 12(2):116-121
Khazaeli et al.		HER010300488-517 "Frequent Anti-V Region Immune Resp. to Mouse…"
LoBuglio & Saleh	1992	Am. J. Med. Sci. 304(3):214
LoBuglio et al.	2000	Deposition Transcript from litigation/interference.
LoBuglio et al.	1989	PNAS USA 86:4220-4224
LoBuglio et al.	1990	HER010300318 Abst. Sub. 3rd Conf. On Radioimmunodetect…
LoBuglio et al.	1991	Adv. In Appl. Of Monoclonal Anti. In Clin. Oncl. Chap. 33 pp. 291-295
LoBuglio et al.	1992	HER010300518 Abst. Sub. ASCO Ann. Mtg, Houston, TX.
Meredith	1990	Protocol: UAC 180 NCI:T89-0144 (NCI/CTEP Sheets)
Meredith et al.	1989	Protocol: UAC 180
Meredith et al.	1990	Protocol: UAC 180 (Amended?)
Meredith et al.	1989	Protocol: UAC 079
Meredith et al.	1990	HER010300313 Abst. Sub. 37th Ann. Mtg. For Soc. Of Nuc. Med.
Meredith et al.	1991	HER010300321 Abst. Sub. ASCO Ann. Mtg, Houston, TX.
Meredith et al.	1991	HER010300322 Abst. Sub. 8th Intl. Hammersmith Mtg, Greece
Meredith et al.	1991	HER010300323 Abst. Sub. 38th Ann. Mtg. Soc. Of Nuc. Med.
Meredith et al.	1991	J. Nuc. Med. 32(6):1162-1168
Meredith et al.	1992	Antibod. Immunoconj. & Radiopharm. 5(1):75-80
Meredith et al.	1992	J. Nuc. Med. 33(1):23-29
Meredith et al.	1992	J. Nuc. Med. 9(33):1648-1653
Meredith et al.	1992	J. Nucl. Med. 33:29
Meredith et al.	1995	J. Nuc. Med. 36:2229-2233
Meredith et al.		HER010300320 Abst. Sub. "Comp. localization of murine and chimeric B72.3…
Meredith et al.		HER010300324 Abst. Sub. 7th Intl. Conf. On Monoclo. Anti. Immunocoj.
Meredith et al.		HER010300434-448 "Effect of Human Immune Resp. on Repeat Courses.."
Meredith et al.		HER010300519-544 "Dose Fraction of Radiolabeled Antibodies in Patients…."
Meredith et al.		Med. Physics "Dosimetry of Solid Tumors"
Meredith et al.	1993	
Meredith et al.	1989	Amended Protocol: UAC 180
Meredith et al.	1990	HER010300097/314 Abst. Sub. 5th Cong. - WFNM&B, Montreal, Canada

Meredith et al.	1990	HER010300099/316 Abst. Sub. 3rd Conf. On Radioimmunodetect…
Primus et al.	1990	Cancer Immunol. & Immunother. 31:349
Whittle et al.	1987	Protein Eng. 1(6):499-505
Yarrenton	2000	Deposition in Interference 104,532
	1990	Status Report w/ Master Order Agreement
	1990	Status Report: Phase I Contract - Cancer Therapy
	1991	Status Report Phase I Contract (NO1-CM-97611)
	1992	Status Report Phase I Contract (NO1-CM-97611)
	1994	Status Report: Phase I Contract - Cancer Therapy Phase 1 Contract - CTEP Program (NO1-CM-97611)
	1990	On Study Registration

It is submitted that the claims of the present application distinguish from the University of Alabama Clinical Trials because the claims of the present application do not read on the use of antibodies that are conjugated to a radionuclide.

Anti-CD20 antibodies

A number of patents have issued to Robinson et al, including U.S. Patents. 5,500,362, 5,721,108 and 6,120,767. A related PCT publication is WO 87/02671. Applicants will refer to the oldest patent, U.S. Patent 5,500,362, for purposes of discussion. According to the examples of the '362 patent, the recombinant antibody was expressed in Sp2/0 cells (see Col. 18, lines 5-11). Thus, it would seem that Sp2/0 cells would be the preferred cell line. Other expression hosts are also mentioned, including yeast. See Col. 9, lines 53-64 where yeast is indicated as being "one preferred host" (Col. 9, line 53) along with bacterial hosts, such as *E. coli*, *Salmonella typhimurium, Serratia marcescens* and various Pseudomonas species (Col. 11, lines 1-8) and mammalian cells PcX63Ag8, Vero cells or CHOK1 (Col. 11, lines 58-63). The '362 patent contains no description of the actual preparation or characterization of an antibody expressed in CHO cells. Likewise, the '362 patent does not teach the method as claimed in the present application. Since this patent does not teach the actual preparation of antibodies in CHO cells, and since it does teach the actual production of antibodies in Sp2/0 cells, one skilled in the art would conclude that Sp2/0 cells would be the cell line of choice.

The following references pertain to anti CD-20 antibodies:

Robinson et al.	1996	USP 5500362
Robinson et al.	1998	USP 5721108
Robinson et al.	2000	USP 6120767
Trial Transcript, 2763:17-2767:16, 2792:21-24, 2793:10-14		

Anti-CEA Antibodies

Various prior art references teach the preparation of chimeric anti-CEA antibodies. These references will be divided into two groups, the "Shively references" and the "Cabilly references".

Shively References

Various anti-CEA recombinant antibodies are reported in various references in which Shively is either an author or a co-author. Some of these references describe expression of the antibodies in either Sp2/0 cells or CHO cells. However, the data for antibodies expressed in Sp2/0 cells is more complete and therefore one must assume that Sp2/0 cells are more preferred. In addition, Dr. Shively testified in a Declaration that he contemplated conjugating these antibodies to a radionuclide before using the antibody for therapy (Declaration of Shively of October 30, 2000) and testified in a deposition that he did not contemplate using his antibodies for immunotherapy, but only radioimmunotherapy because "CEA is a poor target antigen for effector function." (See, Shively Deposition Transcript of January 12, 2001 page 56, lines 18-20). Therefore, the Shively references do not suggest the invention defined by the claims of the present application. These references are discussed in some detail in Cabilly Preliminary Motion 1 and the related Opposition and Reply.

Cabilly References

The Cabilly references include US Patent 4,8176,567, EP 0125023 A1, EP 0125023 B1 and Cabilly et al, PNAS USA 81(11):3273-3277. These references report actual expression of an antibody in *E. coli* cells. Although CHO cells are mentioned, CHO cells are not singled out as being of particular importance. No actual expression is reported in CHO cells. Therefore, these references are less relevant than the Shively references.

The following references pertain to anti-CEA antibodies:

Cabilly et al.	1989 USP 4816567	
Cabilly et al.	1984 EP 0125023 A1	
Cabilly et al.	1991 EP 0125023 B1	
Cabilly et al.	1984	PNAS USA 81(11):3273-3277
Cabilly & Riggs	1985	Gene 40(1):157-161
Shively	1981	Meth. Enzymol. 79:31-48
Shively et al.	1992 USP 5081235	
Shively	2000	Declaration of John E. Shively
Shively	2001	Deposition Transcript of Shively

Neumaier et al., 1990, Cancer Res. 50:2128-2134.

Duda et al., 1990, Surgical Onc. 44:73-77

Campath Antibodies

Prior to October 16, 1991, Campath, an antibody against CDw52, was developed by Medical Research Counsil in Cambridge, United Kingdom. The antibody was engineered and expressed in several different cell lines prior to the humanized IgG1 variant being expressed in Chinese Hamster ovary cells. Predecessors to Campath-1H, other variants of the Campath antibody, were shown to be therapeutic.

The following documents and references pertain to the Campath antibody:

Crowe et al., 1992, Clin. Exp. Immunol. 87:105-110.
Cobbold, 1991, Imm. Letters 29:117-122.
Cobbold & Waldmann, 1984, Nature 308(5958):460-462
Hale, 1983, Mol. Biol. Med. 1:21-334.
Hale, 1990, Progress Report - MRC Wellcome Ther. Antibody Centre
Hale et al., 1988, Lancet 2(8625):1394-1399.
Finnegan et al., 1997, J. Rheumatol. 24(7):1448-1449
Riechmann et al., 1988, J. Mol. Biol. 203(3):825-828.
Riechmann et al., 1988, Nature 332(6162):323-327.
Trial Transcript 2758:1-2762:18, 2807:7-2815:15, 2819:7-2821:7

Herceptin

It is Genentech's assertion that certain work was performed with the Herceptin antibody before the earliest U. S. filing date of the Page application (Trial Transcript 1713:5-1724:12, 2788:5-2792:6).

Rituxan

It is Genentech's assertion that in the fall of 1990, IDEC Pharmaceuticals started working on Rituxan and that Phase II clinical trials started in 1994, or late 1993 (Trial Transcript 1786:9-1787:25)

Anti-human placental alkaline phosphatase antibody

DeWaele, et al, Eur. J. Biochem. Vol. 176, 287-295(1988).
Trial Transcript 2768:12-2770:14.

Therapeutic proteins (other than recombinant antibodies) expressed by and/or glycosylated in CHO cells

Prior to the October 16, 1991 filing date, various proteins (other than recombinant antibodies as used in the claims of the present application) were expressed in CHO cells. Some of these proteins were successfully used to treat human patients prior to October 16, 1991. A summary of these proteins follows.

Genentech asserts that in 1983, Genentech was using *E. coli*, yeast and cell lines (including CHO) to express various proteins (Trial Transcript, 1687:5-15).

Genentech also asserts that in 1983, Genentech was working with DHFR$^-$ CHO cell strain to express proteins. It is asserted that this strain was known to produce high levels of proteins (Trial Transcript 1687:25-1688:25).

Tissue Plasminogen Activator (t-PA)

(Trial Transcript 1695: 13-22, 1780:22-1783:4, 2753:2-2757:25)

Recombinant t-PA was expressed in CHO cells, approved by the FDA and used to treat patients in the 1980s. The t-PA was expressed in a CHO K1 derived cell line that was defective in DHFR.

Hepatitis B Vaccine

(Trial Transcript 1698:14-1699:13)

This vaccine, which involved glycoproteins, was in development in 1983-1984 and was expressed in CHO cells.

Factor VIII

(Trial Transcript 1699:14-1701:16)

Factor VIII is a large glycoprotein. It was expressed in CHO cells in the 1983-1984 time frame (Trial Transcript 1700:16-19)

CD4 IgG/Fragments/Hybrid Immunoglobulins

(Trial Transcript 1701:17-1705:10, 1767:4-1779:17, 2785:2-2788:4)

This group of references includes immunoadhesins, and fragments of antibodies. Some of these molecule were expressed in CHO cells in the late 1980s.

Various references were introduced in the interference (Exhibits 1016-1021, which correspond to USPatents 5,116,964, 5,225,538, 5,336,603, 5,428,130, 5,455,165 and 5,514,582, respectively) describe molecules identified as "hybrid immunoglobulins", "heterofunctional immunoadhesons", etc. These molecules are not antibodies. They are fusion proteins that lack antibody binding domains.

Capon et al.	1992	USP 5116964
Capon et al.	1993	USP 5225538
Capon et al.	1994	USP 5336603
Capon et al.	1995	USP 5428130
Capon et al.	1995	USP 5455165

Capon et al. 1996 USP 5514582
Harris et al 1990 J. Biochem. Vol. 194, 611-620
Sekigawa et al., 1990, J. Virology 64:5194-5198,
Routledge et al., 1991, Eur. J. Immunol. 21:2717-2725,

USP 5605689	1997	Ammann

GP120

(Trial Transcript 1705:11-1707:7, 1779:14-1780:20)

Recombinant GP120 (HIV envelope glycoprotein 120) was expressed in CHO cells. The carbohydrate structure of the expressed protein was studied (Mizuochi et al., *Biochem. J.*, 254:599-603 (1988)).

DNAse

(Trial Transcript 1707:8-1708:13)

DNAse is a Genentech product that was developed in the late eighties. It is a recombinant glycoprotein product that was expressed in CHO cells and was used to treat patients with cystic fibrosis.

Other Proteins and Fragments

(Trial Transcript 1708:17-1713:21)

Other proteins or fragments that were expressed in CHO cells are cited in the references listed below.

Dyer et al., 1990, Leukemia & Lymphoma 2:179-193
Stevenson et al., 1991, Blood 77:1071-1079
Peakman et al., 1994, Hum. Antibod. Hybrid. 5:65-74
Routledge et al., 1991, Eur. J. Immunol. 21:2717-2725,

Information Relevant to Inventorship

During the Interference and the District Court litigation, Genentech questioned whether the designation of inventorship of the Page patents, the parent to this divisional application, was proper. The positions of the parties on this issue are set forth in Cabilly Preliminary Motion 5, the Opposition by Glaxo and the Reply by Cabilly. After considering all information relevant to this issue, applicants have determined that the inventorship of the already issued Page patents (USPS 5,545,403, 5,545,404 and 5,545,405) is proper. It is also believed that Drs. Page and Crowe are coinventors of the claims of the present application. It is also believed that Dr. Rapson is a coinventor (with Drs. Page and Crowe) of claims which indicate that the antibody was obtained by culturing the CHO cells in a serum-free medium. A petition to add Dr. Rapson as a co-inventor will be filed if these claims are retained in the present application.

Information Relevant to Enablement

Genentech has questioned the enablement of the claims of the Page patents. The positions of the parties are set forth in Cabilly Preliminary Motion 4, the Opposition by Glaxo and the Reply by Cabilly. It is Glaxo's position that the claims of the Page patents and the claims of the present application fully comply with 35 USC 112. The claims recite the essential features of the invention. The claimed invention has applicability to various types of recombinant antibodies expressed in CHO cells.

FEES

IV. ☐ THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(b): (check one box)

a. ☐ within three months of the filing date of a national application (37 C.F.R. § 1.97(b)(1)). No fee or statement is required. (This section is not to be used with RCE's and CPA's).

b. ☐ within three months of the date of entry of the national stage as set forth in § 1.491 in an international application (37 C.F.R. § 1.97(b)(2)). No fee or statement is required.

c. ☐ concurrently with the filing of a Continued Prosecution Application under 37 C.F.R. § 1.53(d) or concurrently with the filing of a Request for Continued Examination under § 1.114 (37 C.F.R. § 1.97(b)(4)). No fee or statement is required.

d. ☒ before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b)(3)). No fee or statement is required.
In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the statement under 37 C.F.R. § 1.97(e) below, or, if no statement has been made, charge our deposit account in the amount of $180.00 as required by 37 C.F.R. § 1.17(p).

V. ☐ THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(c): (check one box)

before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c)(1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c)(2)).

a. ☐ No statement; therefore, a fee in the amount of $180.00 as required by 37 C.F.R. § 1.17(p).

or

b. ☐ See the statement below. No fee is required.

VI. PAYMENT OF FEES (check one box)

☐ A check in the amount of $180.00 as required by 37 C.F.R. § 1.17(p) is enclosed for the above-identified fee.

☐ Please charge Deposit Account No. 02-2448 in the amount required by 37 C.F.R. § 1.17(p) for the above-indicated fee. A triplicate copy of this paper is attached.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is requested to consider this IDS under the proper rule and charge the appropriate fee to Deposit Account No. 02-2448.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
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GMM/las
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Enclosures:
☒ PTO-1449
☒ Documents
☐ Foreign Search Report
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☐ Other: